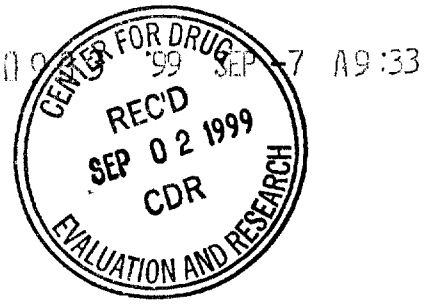
GlaxoWellcome

August 26, 1999



Management Dockets
Dockets Management Branch
Food and Drug Administration
HFA-305, Room 1-23
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket Number: 99D-0529

Dear Sirs:

Please find enclosed GlaxoWellcome's comments on the draft Guidance for Industry – Changes to an Approved NDA or ANDA.

Please feel free to contact me at (919) 483-6408 if you need additional information or clarification regarding the comments.

Sincerely,

Suva B. Roy.

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99D-0529

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Comments from GlaxoWellcome on the Draft Guidance for Industry - Changes to an Approved NDA or ANDA

General Comments

We commend the Agency for its efforts to provide clarity and detail for the proposed revision to 21CFR314.70 but many changes and details listed in this guidance belong in the proposed rule. This document should focus on adding clarity to the proposed rule. We feel that the proposed rule and this document could have further reduced filing requirements by applying the principles of assessing the effects of change on post-change materials when compared to the pre-change materials. Also, in some instances it also appears that the guidance have added new prior-approval submission requirements.

The format of the draft guidance is difficult to follow the use of decision trees and tabular formats may make the guidance more user friendly. The guidance may also be easier to use if it is arranged by submission type such as Prior-approval Supplement (PAS), Changes Being Effected-30 (CBE-30), Changes Being Effected (CBE) and Annual Reports (AR) followed by sub-headings for the type of change such as site change, process change etc.

The document on lines 32-34 the guidance states that it supercedes other guidances. But on lines 36-37 it recommends the applicant to consider all other relevant guidances for information requirement. This is a prescription for confusion and application errors unless the other guidances are cross-referenced to consult this guidance. It may be simpler to refer the reader to the other guidances and the reporting requirements listed there in. As those guidances are revised and updated it will not require simultaneous updating of this guidance as well. We would highly recommend the simpler approach.

We recognize the CBE-30 is a statutory classification, unfortunately it does not provide material advantage over a CBE supplement for both the Agency and the industry. From the Agency point of view the reviewer will be spending time twice on the same application, first for an administrative review for the completeness of the information and later to actually review the application. From the industry point of view the thirty-day wait period does not necessarily provide increased assurance of an approval action. We suggest any change can be the subject of a CBE-30 supplement could just as easily be to the reclassified as a CBE supplement. This will be a time saver for both the FDA and the industry.

Although, reducing reporting requirements using comparability protocols is a good idea in principle, it may also result in significant inconsistencies between applications. We would strongly recommend FDA publishing comparability protocol guidance before implementing this section of the proposed rule.

Throughout the guidance, the term "CDER-approved" is used. Is it the intention of the Agency to publish such lists? Alternatively, if such "CDER-approved" lists do exist, then the guidance should include references to such lists. Also, throughout this guidance the phrase "except as otherwise noted" has been used. It would add to the clarity and user friendliness of the document if the statement cross-references where the exceptions are noted.

The phrases "validate the effects of the change" and "assess the effects of the change" have been used interchangeably throughout the document. Although, the footnote to line 105 clarifies that the term validate in this context is not the same as GMP validation. Nevertheless for clarity we suggest using "assess (ing) the effects of the change" consistently throughout the document.

A statement "Any other changes not specifically listed as the subject of a PAS, CBE-30 or CBE application should be reported in AR." should be inserted either in the Introduction or at the end of each section would clarity.

Specific Comments

61 - 68 - Currently, the Agency does not always acknowledge within 30 days that a submission has been received. Will the Agency issue letters acknowledging the adequacy of the information and suitability of filing for CBE-30 supplements within 30 days? It appears that from a GMP standpoint such a letter will be essential to release a product.

70 - 73 – Revise as "If after review the FDA disapproves a changes being effected in 30 days or a changes being effected supplement, the Agency will work with the applicant to expediently resolve all issues and to assure the continued availability of the product. The Agency may however order the manufacturer to cease distribution of the drugs that have been made using the disapproved change if it poses a significant safety or efficacy risk." This would be consistent with FDA's current policy and is reasonable.

88-89 – States that the applicant must list all changes included in the supplement or annual report in the cover letter. While this makes sense for the cover letter for the supplemental application, it is impractical for Annual Reports. The Annual Reports contain a chronological list of all changes anyway. We recommend that the sentence be revised as "The applicant should clearly list all changes for which an approval is sought in a supplemental application on the cover letter. The chronological list of all changes in the annual report should capture all changes during the year."

102 - 103 - Please clarify the appropriate location of the field copy certification. The wording implies that the certification should be included in the body of the submission. Historically, this statement has been included in the cover letter accompanying the submission. Also, please clarify where the field copy should be sent for a foreign site.

109 - 112 - We suggest submitting only summaries of information developed to assess the change. Full details will be available on request.

112 - 114 - 21 CFR 314.70(d)(3)(iii) specifies the information required for submission in an Annual Report. The proposed data package includes reference to validation protocols and SOPs. These are GMP documentation and are kept on site and are available to the investigators. We recommend deleting reference to 21 CFR 314.70(d)(3)(iii). Requiring AR filing of these add to the requirements it may also conflict with the Field-Center agreement.

116 - 119 and 155 - 157 - The extent of testing required to assure conformance to specifications is not clear. For example, will a drug substance intermediate change require impurity conformance testing all the way to drug product? If so, this appears to be in conflict with BACPAC I, which indicates that no further impurities testing is required once equivalence has been established at any step following the change.

168 - 185 - If a company has determined there are no safety issues, then submission of the change using the typical filing route would be appropriate. The procedure in the draft guidance does not rely on the company's own scientific rationale for making a decision concerning safety if the Agency requires the filing of a Prior Approval Supplement every time an "adverse" effect occurs when making a change.

197 - 201 - Revise as "Changes in sites for which FDA should be notified include those facilities or establishments used to 1) manufacture or process drug products, drug product in-process materials, drug substances or final intermediates for drug substances, 2) package drug products, 3) label drug products and test 4) test drug substance and drug products, drug product in-process materials, and acceptance testing of primary containers, closures and packaging materials for the drug product."

211 - 221 – Delete it is already included in lines 248-252.

213 - 215 - Please provide an example of item (2) "the type of operation used to be performed at the facility but at some time it had been discontinued and is now being restarted". "The type of operation" implies a process and not a process related to a specific product. This can also be a source of confusion for processes associated with campaign manufacturing situations.

219 - For clarity please change "...new site or a refurbished site..." to "...different site..."

244 - The section should be divided into drug product and drug substance sections for clarity. While certain facilities in the drug product manufacture chain may require inspection the same is not true for the drug substance.

248 and 253 - Please provide further clarification for the types of sites affected by this PAS provision. Is this provision applicable to the following sites: drug substance final intermediate manufacturing; drug substance manufacturing; drug product manufacturing; testing sites for either the drug substance, drug product, excipients, starting materials, intermediates, or packaging components; and packaging and labeling of the drug product?

284 - 309 and 328 - 332 - For clarity, a statement indicating that a satisfactory GMP inspection status of the receiving site is necessary should be included such that there is no misinterpretation if the previous section of the guidance is not reviewed.

333 - 334 - The floor plan is a GMP matter and do not belong in an NDA. This should be deleted.

335 - 336 - "Improvements to manufacturing areas that provide greater assurance of quality" is again a GMP issue and do not belong in this guidance. This should be deleted.

391- 401 – These changes can be reduced to CBE with revalidation of the changes.

408 - 413 - Please clarify if these changes are applicable for both drug product and drug substance.

413 - The filing requirement for this type of filtration change is too restrictive. This change can be a CBE supplement.

414 - This statement should be located under line 415 since it specifically speaks to drug substance.

418 - 420 - This statement is too broad and potentially conflicts with BACPAC I. For example, BACPAC I indicates that manufacturing changes that do not involve new intermediates or starting materials can be filed as a CBE supplement. We recommend replacing "may affect" with "change" in the sentence.

431 - 432 - Please clarify if these changes are applicable for both drug product and drug substance final synthesis steps.

481 - 482 - Reference to "except as otherwise noted". Such changes to equipment are not otherwise noted in this document. A cross-reference to the appropriate document such as the SUPAC documents would add clarity.

505 -507 - Revise as "Regulatory specifications are those specifications proposed by the applicant and approved by the FDA for evaluation of a defined characteristic of the drug substance and the drug product, e.g., potency or purity, dissolution, drug release, content uniformity, stability. The specifications in the U.S. Pharmacopoeia/National Formulary (USP/NF) are those legally recognized under section 501(b) of the Act."

509 - 512 - Move the sentence "The applicant may include.....procedure is used" to a separate paragraph. Also insert "alternate procedures are not approved by the agency". This will add to the clarity.

519 - Rephrase as "Replacing a current regulatory analytical procedure or establishing a new regulatory analytical procedure". It covers both situations.

521-531 - Revise as "A change in a regulatory analytical procedure for a drug substance or a drug product that does not provide the same or increased assurance of the identity, strength, quality, purity and potency. For example, a change..... quantitation is higher. Regulatory analytical methods apply only to drug substance and drug product but not to packaging components, final intermediate or starting materials.

538- 539 - Revise as "Any changes in regulatory analytical procedures that provides increased assurance of the identity, strength, quality, purity or potency of the drug substance and drug product." Also, this should be CBE.

We also suggest, minor changes such as editorial changes, equivalent column substitutions, sample preparations, flow rate changes to optimize peak separation, plate development times etc. should be filed in Annual Reports. See line comment for line 577 below.

540-543 - Revise as "A change to a less discriminating analytical procedure or relaxing an acceptance criterion or deleting a specification for the final intermediate or raw materials introduced after the final drug substance intermediate."

544-550 - Delete. This is incorporated in the proposed revision for lines 540-543 above.

551-556 - Revise as "A change to a less discriminating analytical procedure or relaxing an acceptance criterion or deleting a specification for primary packaging components." The remainder of the paragraph in the draft guidance is included in the revision proposed for lines 540-543 above.

558-562 - Revise as "An addition to a specification or changes in non regulatory analytical procedures for the drug substance and the drug product to provide increased assurance of identity, strength, quality, purity or potency."

567- 571 - Delete "that is consistent with FDA requirements" from the sentence. We refer to Sections 201(g) and 501(b) of the FFD&C Act and CDER MAPP 7211.1 dated November 1, 1995.

577 - Add, "Minor changes in analytical procedures, editorial changes, equivalent column substitutions, sample preparations, flow rate changes to optimize peak separation, plate development times etc."

578 - 583 - Revise as "A change in analytical procedure or acceptance criteria or deleting a specification for the starting materials; raw materials introduced before the final drug substance intermediate; and drug substance intermediates before the final intermediate." Identity, strength, quality and purity or potency is more appropriately associated with the drug substance and drug product itself therefore does not belong here.

584- 585 - Delete the sentence. Reference standards are certified materials against which samples are tested. The information is included in the NDA submission and is rarely ever updated after the NDA approval. However, a change from an in-house reference standard to a compendial reference standard may be an AR item.

588- 606 - The general considerations here appears to be very different from the approach in the recently issued Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics. The sentences on lines 590-595 "In some cases there is .....an important test may not have been performed to rule out such effects" is disconcerting. If this is truly FDA's concern perhaps the guidance should include lists of tests that should be undertaken for each type of change and cover all possible change scenarios. This section on general considerations should be rewritten.

616 and 619 - States "never been approved by CDER for that particular dosage form...". This unclear, does this imply that the FDA has approved packaging components, inks and adhesives universally suited for particular dosage forms? For example, if the CDER has approved a specific combination of packaging component for a oral solution that same combination will acceptable for all oral solution products? Perhaps the replacing "product" for "dosage form" may be more meaningful.

621 - Please clarify whether HDPE is a considered a semi-permeable container for this type of change?

622- 624 - Examples of primary packaging components that control or modify the dose delivered would add to the clarity.

638 - 639 - Changes in the shape and size of the container by has minimal potential for change. This can be the subject of a CBE supplement with the showing of continued sterility assurance under the same processing conditions.

640 - 641 - Examples of secondary packaging components that provide additional protection would be helpful.

651 - 652 - Revise as "A change in the size and/or shape of a container for a non-sterile drug product, except for solid dosage forms, or from one container closure system to another."

661 - 662 - Revise as "A change in the size and/or shape of a container for a non-sterile solid dosage form without a change from one container closure system to another."

668 - 669 and 690 – 691 - Add tamper evident cap.

672- 673 - Revise as "Changes in packaging materials used to control odor or moisture (e.g. charcoal, silica gel packets)."

715 - Inclusion of time frames for the submissions of various types of labeling change would add clarity. We recommend the adoption of current FDA timelines specially as it relates to the addition of adverse events or precautions.

736-737 – Change to a more restrictive labeled storage condition, due to stability considerations such reducing temperature from 30° to 25°C, or adding an additional precaution statement like "Protect from moisture" should only be the subject of a PAS.

776 - 777 - Addition of examples of change that may affect product sterility assurance would be helpful.

779 - 781 - Revise to delete "based on pilot scale batch data". This is contrary to the ICHQ1A, which allows setting of expiry date based on pilot scale batches.

784 – Permanent reduction in expiry for stability considerations should be the subject of CBE supplement.

793 – Revise as "Addition of time points to the annual stability protocol or deletion of time points after significant body of information has been acquired. Switching to ICH storage conditions."